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Biochimica et Biophysica Acta 1745 (2005) 287 – 299
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
http://www.elsevier.com/locate/bba

Review

Signaling via NF-κB in the nervous system

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Received 9 March 2005; received in revised form 20 May 2005; accepted 23 May 2005
Available online 16 June 2005

Abstract

Nuclear factor kappa B (NF-κB) is an inducible transcription factor present in neurons and glia. Recent genetic models identified a role for NF-κB in neuroprotection against various neurotoxins. Furthermore, genetic evidence for a role in learning and memory is now emerging. This review highlights our current understanding of neuronal NF-κB in response to synaptic transmission and summarizes potential physiological functions of NF-κB in the nervous system. This article contains a listing of NF-κB activators and inhibitors in the nervous system, furthermore specific target genes are discussed. Synaptic NF-κB activated by glutamate and Ca^{2+} will be presented in the context of retrograde signaling. A controversial role of NF-κB in neurodegenerative diseases will be discussed. A model is proposed explaining this paradox as deregulated physiological NF-κB activity, where novel results are integrated, showing that p65 could be turned from an activator to a repressor of anti-apoptotic genes.

Keywords: Transcription factor; Neuron; Neuroprotection; Memory; Tumor necrosis factor; Calcium; Synapse; Retrograde; Inhibitor; Activator; Target gene; NF-κB; IκB

1. NF-κB activation via tumor necrosis factor (TNF)

Nuclear factor kappa B (NF-κB) was discovered by David Baltimore's laboratory as an inducible transcription factor in lymphocytes [1]. The so-called canonical pathway of NF-κB activation via tumor necrosis factor (TNF) [2,3] will be presented to summarize part of the general knowledge on activation mechanisms (see Fig. 1). The TNF pathway is one of the best characterized NF-κB-dependent pathways with more than 70 000 references in PubMed. Therefore, we have chosen this so-called canonical pathway, which is also operating in the nervous system, to introduce the NF-κB activation.

Within the nervous system, TNF (a 17 kDa protein) can bind to TNF receptors (TNF-Rs) expressed on both glia and neurons [4]. The expression of the TNF-α gene is subject to autoregulation via activated NF-κB [5]. Two different receptors, p55 (TNF-R1) and 75 (TNF-R2), have been identified. The p55 receptor is thought to be the major NF-κB activating TNF-R [6].

Central to NF-κB activation seems to be the IκB kinase complex (IKK), which is catalyzing the signal-dependent phosphorylation of the NF-κB inhibiting IκB. Thus, the IKK complex initiates NF-κB activation via phosphorylation of IκB, which is a signal for polyubiquitination and subsequent degradation. An amazing wealth of information has been accumulated, describing how receptor activation might be connected to IKK activation. There are themes of ubiquitination after the activation of the trimeric TNF receptor. The binding of soluble or cell-bound TNF leads to the activation of the latent trimerized TNF receptors. These receptors share an intracellular so-called death domain (DD) with several other TNF receptors such as TRAIL receptors or DR3, DR6 and various other receptors with non-TNF ligands such as the CD 95 (Apo/Fas) receptor or the p75 low-affinity nerve growth factor receptor. TNF-RI is unique in its composition of intracellular interaction proteins [7]. The genetic ablation of TNF-R1 (p55) exacerbates traumatic brain injury and correlated with a reduced NF-κB activation [4]. Recent data suggest that the TNF-R2 is responsible for a persistent NF-κB activation and neuroprotection [8,9].

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doi:10.1016/j.bbamcr.2005.05.009

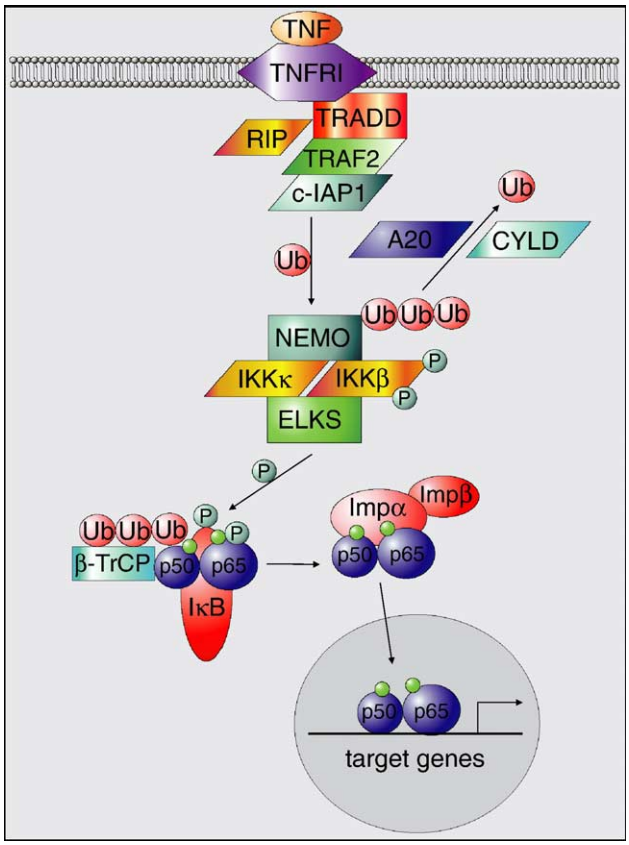

Fig. 1. Canonical pathway of NF-κB activation by tumor necrosis factor (TNF). The activation of the TNF receptor by ligand binding is transmitted to the IKK complex which phosphorylates IκB family inhibitory molecules (see text for details). This targets IκB for polyubiquitination and subsequent degradation within the 26S proteasome. This frees nuclear localization signal on the DNA-binding p65/p50 subunits. After nuclear import, target gene transcription is initiated. Not all signaling components depicted in the canonical pathway have been investigated in the nervous system, but appear to be present in neurons and glia. Proteins are depicted as icons which illustrate a functional category (receptor, enzyme, etc.) as suggested by the Alliance for Signalling convention (www.signaling-gateway.org). Ub=ubiquitination; P=phosphorylation.

The trimerization of the non-signaling TNF-R complex is mediated by a N-terminal pre-ligand assembly domain. TNF binding activates the pre-assembled receptor trimer via release of silencer of death domains (SODD) from the intracellular death domains; see [7] for discussion. The physiological role of SODD remains unclear. The trimeric death domains seem to function as an assembly platform for further intracellular interactors such as the adapter protein TRADD. TRADD seems to enable a bifurcation in either the apoptotic pathway, leading to caspase activation, or in the anti-apoptotic NF-κB-dependent pathway, which involves the transcription of genes encoding survival factors. Apoptosis, as well as anti-apoptosis, is involving TRADD in the context of different signaling complexes [10]. The initial receptor-bound complex (see Fig. 1) might contain TRADD, RIP and TRAF2. This provides a signaling scaffold for the activation of NF-κB. An apoptotic pathway could be triggered by FADD, which might interact with RIP and TRADD in a non-receptor bound cytoplasmic complex. With its N-terminal domain, TRADD could facilitate the interactions with TRAF1 and TRAF2. Anti-apoptotic proteins are targeted to the receptor complex, e.g. cIAP-1 and cIAP-2. This might be the reason for the relative good protection of activated TNF-R1 signaling against apoptosis. Several studies with murine neuronal cultures use human TNF-α, which has been shown to activate the TNF-R1 [11,12].

The IκB kinase complex might integrate many NF-κB activating stimuli culminating on NF-κB activation within the nervous system such as TNF, LPS, IL-1, NGF or glutamate-mediated signaling; see [13] for a review.

Crucial for NF-κB activation is the phosphorylation of IκB. This is most commonly due to the interaction of activated IκB–kinase complex (IKK) with IκB. The IKK complex is composed of two catalytic subunits (IKK-α and IKK-β), a receptor targeting/oligomerization subunit NEMO and ELKS, a recently discovered IκB-α targeting subunit [14]. The activation of the IKK complex might be regulated by multiple mechanisms [2]. A classical phosphorylation of an activation loop has been reported for the main IκB phosphorylating kinase IKK-β at serines 177 and 181 [15]. This might be either due to autophosphorylation or due to upstream kinases. Surprisingly, only for the upstream kinase MEKK3 genetic evidence for an involvement in the TNF pathway could be provided [16]. Other activation mechanisms dependent on the oligomerization of the IKK complex have been described [17,18]. NEMO-mediated recruitment of the IKK complex to the T cell receptor complex has been identified as activation mechanism [19]. Surprisingly, also the membrane localization of NEMO could activate the IKK complex [19]. NEMO, the regulatory subunit of the IKK complex, is inducibly ubiquitinated. The receptor-bound complex containing TRAF2 and TRAF5 could recruit the IKK complex to the membrane-bound TNF receptor and thus lead to activation via IKK oligomerization [20]. IκB is recruited to the IKK complex via an interaction with ELKS [14]. The activated IKK complex could catalyze the phosphorylation of Ser 32 and 36 on the IκB-α molecule.

As summarized above, the activation of the IKK complex seems to rely on multimerization. The ubiquitination of NEMO might be an essential prerequisite of the activation process, since deubiquitinating enzymes such as CYLD [21,22] are essential to deactivate the IKK complex. These ubiquitination pathways seem to be independent of the proteasomal degradation but are modulating oligomeric state. Other deubiquitination and ubiquitination activity is found to be encoded in the protein A20, which could target RIP for degradation [23].

For an extensive review of the ubiquitin–proteasome system, see the special issue of BBA, Vol. 1695 (2004). Ubiquitin (Ub) is a small (86 kDa) protein used to tag proteins either for the degradation or for signaling (multimerization). Ubiquitin is conjugated to the amino groups of lysine residues on target proteins by a cascade of enzymes called E1, E2 and E3 [24]. An SCF (Skp-1/Cul/F box)-type

multisubunit E3 ubiquitin ligase holoenzyme contains the phospho-IκB specific acceptor subunit bTrCF and is responsible for IκB poly-ubiquitination [25]. Interestingly, one of the frequently used pharmacological inhibitors of NF-κB activation pyrrolidone dithiocarbamate (PDTC) acts as an inhibitor of the IκB ubiquitin–ligase complex [26]. The signal for the ubiquitin–ligase seems to be the phosphorylation of serines 32 and 36 on IκB-α.

IκB proteins are essential regulators of nuclear import, which can interact with the nuclear localization signal (NLS) to induce an alpha helical conformation [27,28]. Interestingly, IκB-α only interacts with the NLS of p65, whereas IκB-β interacts with both the NLS of p50 and p65 [29]. This conformation cannot be recognized by the nuclear import receptor importin alpha [27], in contrast, IκB free nuclear localization signal assumes a random coil conformation, which is the basis for the interaction with importin. Recently, it was shown that the NLS of p50 and p65 were recognized mainly by importin α3 [30]. A fresh view on import/export suggests additional complexity since the trimeric p50/p65 IκB-α complex is shuttled between nucleus and cytoplasm [29]. The nucleocytoplasmic shuttling of the trimeric complex of p50, p65 and IκB-α could not be observed by [30]. In addition to inhibition by IκB, there seems to be a novel mechanism to terminate NF-κB signaling: promoter-specific degradation of p65 via nuclear proteasomes [31].

2. NF-κB subunits

Inducible NF-κB resides in the cytoplasm in a latent DNA-binding form (see Fig. 1: blue p50 and p65 molecules). So far, five DNA-binding isoforms have been described: RelB, c-Rel, p65 (RelA), p50 and p52, the latter two being proteolytic products of larger precursors. Surprisingly, p50 and p52 are products of specific protein degradation within the proteasome. In some proteins, the proteasome only degrades specific parts of the protein and leaves the rest intact. This process, named regulated ubiquitin proteasome-dependent pathway (RUP), was recently reviewed by [32]. The C-terminal part of the NF-κB p50 precursor p105 is degraded by the proteasome in RUP-dependent manner. Degradation occurs either co- or posttranslationally. Mechanistically, a protection of degradation via dimerization has been suggested. Interestingly, the dimerization of NF-κB can already occur between two nascent polypeptide chains emerging from successive ribosomes on the mRNA [33]. This complex way of processing might add further ways of regulation, especially in neurons where proteasome activity seems to be regulated by synaptic activity [34]. The NF-κB subunits Rel-B, c-Rel and p65 (RelA) contain transactivating domains that are capable to activate transcription without the help of other NF-κB subunits. DNA-binding occurs as a dimer, whereas the latent non-DNA-binding NF-κB complex contains an inhibitory subunit called IκB. Later on, more IκB subunits were described. Well-characterized inhibitory subunits are: IκB-α, IκB-β, IκB-γ(p105), IκB-δ(p100) and IκB-ε [35].

3. NF-κB within the nervous system

Central functions of the nervous system are information transmission, processing and storage. To fulfill these elaborated demands, special cellular structures have been evolved. Neurons are able to receive, transmit and store information. Two neurons can communicate via synapses, which are specialized cellular compartments, consisting of a presynaptic (sending) cell and a postsynaptic (receiving) cell. Frequently, chemical synapses (see Fig. 2) are used to communicate within the neuronal networks. Other important cell types are summarized as glia (neuronal glue). These cells can assist or participate in synaptic information processing. Neurodegeneration can destroy subcellular structures such as synapses and/or lead to neuronal cell death. Neuroprotective processes include calcium buffering, generation of novel synapses, anti-apoptotic gene expression, caspase inhibition, balancing of reactive oxygen intermediates, etc., thus protecting neurons from neurodegeneration.

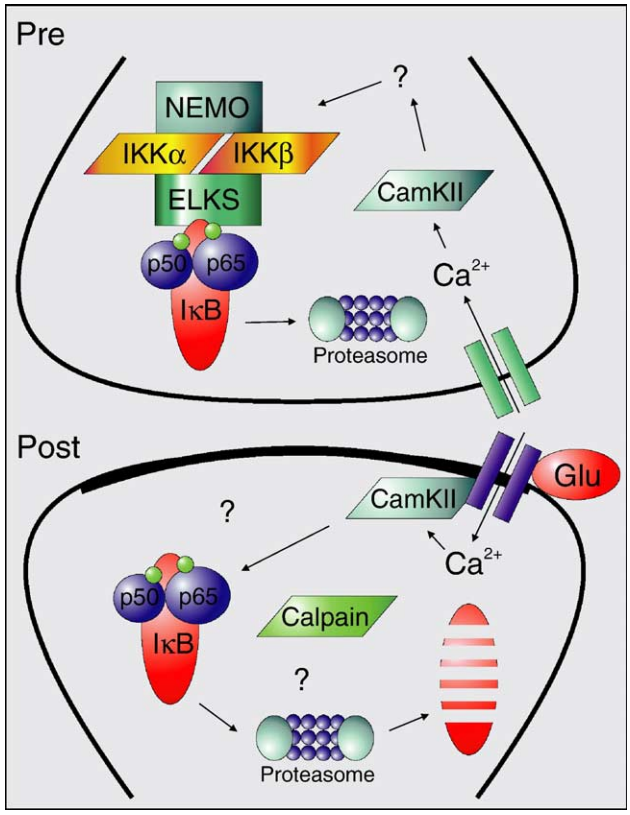

Fig. 2. Localization of the NF-κB activation machinery within the synapse. Both pre- and postsynapse seem to contain the necessary components. The importance of pre- and postsynaptic activation mechanisms has to be clarified.

Table 1
Examples for molecules activating NF-κB in the nervous system

Molecule	Cell type	Reference
Glutamate	Neurons	[42]
Kainate	Neurons	[41]
NMDA	Neurons	[52]
TNF	Neuroblastoma	[53]
TNF	Neurons	[54,55]
TNF	Astrocytes	[56]
TNF	Microglia	[57]
IL-1	Glia cells	[13]
IL-1	Neurons	[58]
sAPP	Neurons	[59]
sAPP	Microglia	[60]
Aβ	Neurons	[43,61]
Aβ	Astrocytes	[43]
Aβ/IFN γ	Microglia	[62]
ATP	Microglia	[63]
ATP/IL-1	Astrocytes	[64]
Adenosine	Neurons	[65]
LPS	Microglia	[66]
LPS	Astrocytes	[67]
EPO	Neurons	[68]
Bradykinin	Neurons	[69]
SDF-1	Astrocytes	[70]
EGF	Astrocytes	[71]
VEGF	Neuroblastoma	[72]
NGF	Neurons	[73]
NGF	Schwann C.	[49]
NGF	Oligod.	[74]
CNTF	PNS neurons	[75]
LIF	PNS neurons	[75]
IL-6	PNS neurons	[75]
CT-1	PNS neurons	[75]
BDNF	Microglia	[50]
NT-3	Microglia	[50]
NT4/5	Microglia	[50]
IGF-1	Neuroblastoma	[76]
ADNF	Neuroblastoma	[77]
PEDF	Neurons	[78]
H_2O_2	Neurons	[55]
H_2O_2	Oligodendrocyte	[79]
Gangliosides	Neurons	[80]
Glutaredoxin	Neurons	[81]
Focal cerebral ischemia	Neurons	[82]
Injury	Neurons	[130]
RAGE dependent diabetic neuropathy	Neurons	[83]
Non-Aβ amyloid	Neurons	[84]
Amitriptyline	Neurons	[85]
Desipramine	Neurons	[85]
Fluoxetine	Neurons	[85]
IL-1	Neurons	[86]
Lack of prion protein	Neurons	[87]
Selenium deficiency	Neurons	[88]
Intracellular calcium	Neurons	[89]
AMPA	Neurons	[90]
BDNF	Neurons	[91]
NGF	Neurons	[91]
NT-3	Neurons	[91]
NT-4/5	Neurons	[91]
Pre-myelination	Schwann cells	[92]
Dehydroepiandrosterone (DHEA)	PC-12	[93]
Allopregnanolone (Allo)	PC-12	[93]
Sleep deprivation	Neurons	[94]
FAIM	Neurons	[95]
TGF-β1	Neurons	[96]

Within the nervous system, inducible NF-κB is most frequently composed of 2 DNA-binding subunits (e.g., p50 or p65) that are either constitutively active or form a complex with the inhibitory subunit IκB-α [36–43]. There are reports of other κB-binding activities such as brain-specific transcription factor (BETA) specifically detected in grey matter extracts [44], developing brain factors (DBFs), which were reported to be highly enriched in developing cortex [45] and neuronal κB binding factor (NKBF) with different target sequence requirements [46]. These κB binding factors were not assigned to specific genes, nor could they be tested directly in reporter gene assays. On the other hand, it seems to be granted that there is an additional level of complexity, added by overlapping mutually exclusive or synergistically acting binding sites for other transcription factors. In glia and neurons, a sustained NF-κB activation for up to 72 h was observed. Novel data suggest that this might be due to a differential use of IκB isoforms α and β. For glial cells, it was reported that sustained NF-κB activity induced via IL-1 was still present even after IκB-α protein amount was returned to the level measured before stimulation, whereas IκB-β protein levels remained low, suggesting that IκB-β is the negative regulator for sustained NF-κB activation [47]. In contrast, a biphasic response which is repressed by IκB-α was reported for TNF-stimulated neural cells [48]. Whereas a lot of knowledge on the mechanisms of TNF-mediated signaling has been accumulated from non-neuronal cells, a systematic analysis of the TNF pathways within the nervous system has not been done so far.

4. Activators of NF-κB within the nervous system

Many activators of NF-κB were identified (Table 1), some with specificity for the nervous system such as the neurotransmitter glutamate acting as an NF-κB activator via the main ionotropic glutamate receptors or the neurotrophins, which display an amazing specificity: NGF is activating NF-κB via the p75 receptor [49], whereas other neurotorphins such as NT-3 or NT4/5 do not activate NF-κB. In microglia, all neurotrophins do activate NF-κB [50]. Taken together, there is a lot of complexity in the system: One molecule like TNF can activate or repress NF-κB in neurons [51], and there are cell-type specific effects.

5. Inhibitors of NF-κB within the nervous system

There are anti-inflammatory cytokines which are known from the immune system like TGFβ or IL-10 which also

Notes to Table 1:
NMDA: *N*-methyl-D-aspartate; TNF: tumor necrosis factor; IL-1: interleukin-1; sAPP: secreted beta-amyloid precursor; Aβ: beta-amyloid; IFN γ: interferon γ; LPS: lipopolysaccharide; EPO: erythropoietin; SDF-1: stromal-derived cell factor-1 alpha; EGF: epidermal growth factor; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

inhibit NF-κB in the nervous system (see Table 2). Mechanistically, it is less clear how these molecules act in the nervous system. One possibility might be the induction of IκB transcription [97]. Some molecules are already known as activators, but seem to act in higher concentration as repressors. Interestingly, the lipid peroxidation product 4-hydroxy-2,3-nonenal inhibits both constitutive and inducible NF-κB activity [98].

6. Target genes within the nervous system

In a heroic effort, H.L. Pahl compiled 150 stimuli and 150 target genes of NF-κB [123]. This ever growing list of target genes, mainly in non-neuronal cells, is updated on T.D. Gilmore's webpage (www.nf-kb.org). A limited number of genes regulated by brain NF-κB and with direct relevance for the nervous system have so far been described [124]. These include the neural cell adhesion molecules [125], inducible nitric oxide synthase [126], amyloid precursor protein [127], μ-opioid receptors [128], brain-derived neurotrophic factor [52], inducible cyclooxygenase 2 (Cox II, [129]) and Ca^{2+}/calmodulin-dependent protein kinase II (CamKIIδ [130]).

Table 2
Examples for molecules repressing NF-κB in the nervous system

Molecule	Cell type	Reference
IL-4	Astrocytes	[99]
IL-10	Astrocytes	[99]
IL-10	Neurons	[100]
IL-10	Microglia	[101]
TGFβ	Microglia	[102]
TGFβ	Neurons	[103]
TNF/H_2O_2	Neurons	[104]
TNF	Neurons	[55]
NO	Neurons	[105]
NO	Microglia	[106]
Hydroxy-nonenal	Neurons	[98]
Glucocorticoids	Neurons	[107]
Aβ	Neurons	[43]
Melatonin	Neurons	[108]
Corticotropin-releasing-hormone	Neurons	[109]
Aspirin	Neurons	[58]
Triflusal	Glia	[110]
LY341122	Neurons	[111]
Ganglioside	Astrocyte	[112]
PDTC	Neurons	[41]
PDTC	Microglia	[66]
Vit E	Neurons	[113]
Dexanabinol (cannabinoid)	Neurons	[114]
Hypericin	Neurons	[115]
Selegiline	Neuroblastoma	[116]
Methylpyridinium (MPP(+))-	Neuroblastoma	[117]
Silymarin	Microglia	[118]
Mutant preseniline-1	Neurons	[119]
Caffeic acid phenethyl ester (CAPE)	Neurons	[120]
Selenite	Neurons	[121]
BAY 11 7082	Neurons	[122]

To our knowledge, there are only few studies analyzing NF-κB-dependent gene expression in the nervous system on larger scales. In a microarray study using U373 human glioblastoma cells, many genes responded to TNF (>880 from 7500 tested) and were measured with a more than two-fold induction rate [131]. In this study, several novel TNF-responsive genes (about 60% of the genes regulated by a factor >3) were detected. A comparison of TNF-induced gene expression profiles of nervous system derived U373 cells, with profiles from non-nervous system 3T3 and Hela cells revealed striking cell-type specificity. Several of the TNF-induced genes were repressed by the inhibitor of IKK: PDTC and might therefore constitute novel target genes. It is not easy to discriminate between a role for NF-κB in glia or neurons in vivo. Cell-type specific knockout models might help to clarify this issue. Recently, a study using brain ischemia could discriminate between astrocytic and neuronal NF-κB activation. The transgenic expression of trans-dominant IκB-α by a neuron-specific NSE promoter resulted in a reduction of ischemic cell death, whereas the expression of IκB in astrocytes did not reduce the infarct size [132]. These data argue against the neuroprotective role of NF-κB in ischemia, but it might be considered that brain reperfusion following ischemia can lead to a widespread inhibition of neuronal protein synthesis. Thus, the transcription factor NF-κB might execute its function before brain ischemia. Here, we propose that the inhibition of neuronal NF-κB might act in a similar way as ischemic preconditioning, thus fortifying neurons against ischemic stress.

On the other hand, under pathological conditions, the anti-apoptotic role of NF-κB might be reversed into a pro-apoptotic function. Recent data suggest that p65 can be switched from an activator into a dominant repressor of transcription in a promoter-specific manner [133]. The p65-mediated transcription of anti-apoptotic genes through the recruitment of co-activators (histone acetyltransferases) promotes survival under physiological conditions. Under pathophysiological conditions, p65 is switched to a promoter selective dominant repressor of anti-apoptotic genes. This switch to a repressor might be mediated by the recruitment of co-repressors (histone deacetylases).

7. NF-κB and neuronal synaptic plasticity

It has been proposed by Aryeh Routtenberg [134] that synaptic plasticity leads to information storage as the result of a synaptic dialogue. The first step would be glutamate release from the presynaptic site, followed by a modification of the presynaptic release process. This process is thought to require a retrograde messenger, which travels along the axon to switch on gene expression, in order to replenish presynaptic protein supply. We and others think that NF-κB might be crucially involved in this important process of synaptic plasticity. In the following,

we will shortly review the evidence accumulated so far (see Fig. 2).

The capability of NF-κB in transmitting information from active synapses to the nucleus is supported by several studies demonstrating the presence of NF-κB in synapses [36,135,136]. Synaptosomes contain presynaptic proteins that are sealed and stabilized by the postsynaptic density. Inducible forms of NF-κB have been found in synaptosomal preparations [36]. Low-salt extracts prepared from synaptosomes contain NF-κB proteins, such as p50 and p65, together with IκB-α. Synaptophysin cofractionates with NF-κB proteins during purification. The colocalization of synaptophysin and NF-κB proteins has also been detected in rat cerebral cortex [36]. In cortical extracts, NF-κB DNA-binding could be activated by the detergent desoxycholate (DOC), resulting in 2 specific DNA-binding complexes with different sensitivities for DOC. Super-shifting and inhibition with recombinant IκB-α showed a bona fide DNA-binding complex that includes the p65 and p50 subunits. Similar complexes were detected using hippocampal synaptosomal preparations [135,136]. In addition, Meberg and coworkers reported a robust increase of p65 mRNA after long-term potentiation, in vivo. It is possible that this is part of a feed-forward mechanism leading to increased DNA-binding to κB elements during long-term potentiation. Recently, also an important influence of NF-κB on long-term suppression of synaptic transmission was reported [137]. Purkinje cell synapses were analyzed using light microscopy and en passant synapses were found to contain NF-κB [42]. Using electron microscopy, NF-κB- and IκB-α-like immunoreactivities within dendrites, including dendritic spines and postsynaptic densities, of neurons in the hippocampus and the cerebral cortex [138] were reported. With the help of an activity-specific anti-p65, antibody activated NF-κB was detected in granule cell dendrites within the fascia dentata of rat hippocampus [139]. NF-κB is activated in neurons by glutamate and depolarization [41,42]. In *Drosophila melanogaster*, the NF-κB homolog Dorsal colocalizes with the IκB homolog Cactus within the nervous system. Both proteins are detected at high levels in postsynaptic sites of glutamatergic neuromuscular junctions [140]. Thus, NF-κB is utilized as a retrograde messenger in both pre- and postsynaptic compartments (see Fig. 2). Memory consolidation in crab also involves the activation of NF-κB-like activity [141]. Activated NF-κB was detected in Aplysia axons [142] and in rat [143]. In rat, traumatic brain injury first an activation of axonal NF-κB and later activated NF-κB is detected in neuronal nuclei. Activation could be detected as long as 1 year after brain injury [144]. As a potential injury or stress signal, sensed by synapses, in the vicinity of diffuse plaques, neurons show activated synaptic NF-κB [145]. This might explain the activation of NF-κB in neurons around diffuse plaques, which is lost in neurons around later plaque stages [51]. Recently, the transport of NF-κB in living neurons was analyzed [136,146]. To enable analysis of translocation of GFP-tagged p65 in living hippocampal neurons, a GFP tag was fused to the p65 subunit of NF-κB and confirmed that this fusion protein (GFP-p65) retained its functionality as a transcription factor. GFP-p65 was present in the nuclei of neurons, but after overexpression, together with IκB-α the distribution of the protein switched from nuclear to neuritic (in dendrites and axons). In glutamate-stimulated hippocampal neurons, a return of GFP-p65 from a neuritic to a nuclear distribution was observed. Meffert and colleagues reported a similar result [136]. Glutamate-induced movement of GFP-p65 was detected in hippocampal neurons. When using low amounts of GFP-p65 expression vectors, endogenous IκB was able to keep the fusion protein in neuritic/cytoplasmic localization. Glutamate agonists could overcome the localization to neurites and activate a nuclear localization. Synaptic localization was crucially dependent on p65 [136]. In KO p65 animals, which are viable when crossed to a TNF-RI background, no synaptic NF-κB activity was detected [136]. Interestingly, the redistribution of GFP-p65 was dependent on a functional nuclear localization sequence (NLS) [146]. This NLS-dependent retrograde transport was already described for Aplysia axons [147]. Recently, it was reported that axonal injury leads to increased retrograde transport of NLS peptides [148]. This transport was mediated by an importin α/β complex interacting with the retrograde motorprotein dynein [148]. NF-κB activation by the neurotransmitter glutamate was identified [41,42,89,149] in cerebellar granule cells. The constitutive activity of NF-κB was initially identified within neurons from the hippocampus and the cerebral cortex, using EMSA and immunofluorescence with an antibody specific for the activated p65 and with reporter gene assays [36,39,150–152]. It was suggested that constitutive NF-κB activity is the result of synaptic activity [13,39,41]. The basal constitutive NF-κB activity in neurons could be repressed by specific inhibitors, of action potential generation, glutamate receptors and L-type calcium channels [136]. The blockade of constitutive active NF-κB was most effective through the inhibition of *N*-methyl-D-aspartate (NMDA) receptors using APV. The blockade of L-type calcium channels with nimodipine was also effective. This suggests that extracellular influx of Ca^{2+} either through NMDA receptors or via L-type Ca^{2+} channels could activate NF-κB. Fig. 2 depicts potential pre- and postsynaptic activation mechanisms for NF-κB. There are some evidences for the presynaptic NF-κB activation machinery. The proteasome and ubiquitination enzymes could be detected in the presynapse [153]. Presynaptic mechanisms might involve the localized action of the IKK complex and voltage-gated Ca^{2+} channels, activated during action potential propagation. Calcium ion-mediated activation of calcium/calmodulin-dependent protein kinase II (CaMKII) is present in the presynapse [154]. Also, within the postsynapse, a potential NF-κB activation machinery is in place. Activation by NMDA suggests a postsynaptic signaling where at least some isoforms of CamK (mainly isoform 2) have been reported to be associated with the NMDA receptor. The

autophosphorylation of αCaMKII at Thr 286 by Ca^{2+} influx through NMDA receptors [155] switches the kinase into a calcium/calmodulin-independent active status. It has been shown that CamKII can activate NF-κB in the neurons [89,136]. The way of NF-κB activation by CamK is not solved so far. A contribution of the proteasomal degradation machine seems likely. Indeed, an activation of the post-synaptic proteasomal degradation has been shown after the induction of neuronal activity [34]. The role of calpain remains conflicting, it seems to be active in IκB degradation in cerebellar granule cells [156] but not in matured hippocampal cultures [136].

The activation of NF-κB by glutamate in the cerebellum and the constitutive activity within the basal forebrain neurons could be also detected in mice containing NF-κB reporter genes [149,150,152]. There are some reports on the failure of NF-κB activation in neurons by glutamate [46]. A potential reason for these negative results might be the inverted U-shaped activation curve of NF-κB (see [51] and discussion) or the sensitivity of the EMSA method which could be only used to detect activated NF-κB in brain neurons, when isolated nuclei were prepared [39]. Another reason for these conflicting results might be the use of different culture conditions.

We conclude that NF-κB is capable of being a signal transducer, transmitting information from, e.g., active synapses to the nucleus, in addition to its well-known role as a transcription factor. NF-κB transduces in this manner a synaptic signal into a transcriptional event.

8. NF-κB in learning and memory

NF-κB might be involved in translating short-term signals from distant sites in neurites into long-term changes in gene expression, which may play a key role in plasticity, development and survival. Indeed, it has been shown that p65 −/− on a TNF-RI −/− background results in a severe learning deficit [136]. There are two other mouse models where NF-κB was repressed via tetracycline-regulated expression of transdominant negative IκB: (1) a model with CamKII promoter-driven expression of tTA in basal forebrain neurons [151]; (2) a model with prion promoter-driven tTA expression in neurons and glia by WC Greene's group (see [157]). Both have a modulation of learning and memory. For an extensive discussion, see the recent comprehensive review by [124]. In accordance with Meffert and coworkers, we have found that the repression of NF-κB by IκB in neurons resulted in behavioral deficits and a reduction in LTP and LTD induction. These effects could be correlated with a strongly reduced CREB phosphorylation [172]. On the other hand, IκB expression driven by the prion promoter-expressed tTA resulted in enhanced learning in older animals (WC Greene and coworkers, see [124]). These might be two sides of the same coin. On one side, a repression of neuroinflammation in elder age via the inhibition of pathological NF-κB hyperactivation might enhance learning. On the other side, neuronal NF-κB at physiological levels is needed for learning.

9. NF-κB in neuroprotection and neurodegeneration

Initial reports of the neuroprotective role of TNF [11] were followed by a neuroprotective role for NF-κB. DNA decoy with NF-κB binding sites did compete in cultured neurons with NF-κB activity induced by TNF and did abolish neuroprotection [54,158]. Similarly, survival of adult sensory neurons is dependent on TNF-mediated NF-κB activation [159]. In cerebellar granule cells, which have a low basal NF-κB activity [41], an inverted U-shaped dose response for TNF-mediated NF-κB activation could be detected. Also an inverted U-shaped protection curve was also reported, when TNF-mediated protection against NMDA excitotoxicity [12] was analyzed. Initially it was shown that TNF-mediated signaling via NF-κB could protect neurons against excitotoxic stress and against neurotoxic amyloid β [11,51,54]. The main component of amyloid β consists of a 40- to 43- amino acid peptide, Aβ [160], which is derived from a proteolytic cleavage of a family of ubiquitously expressed trans-membrane proteins,

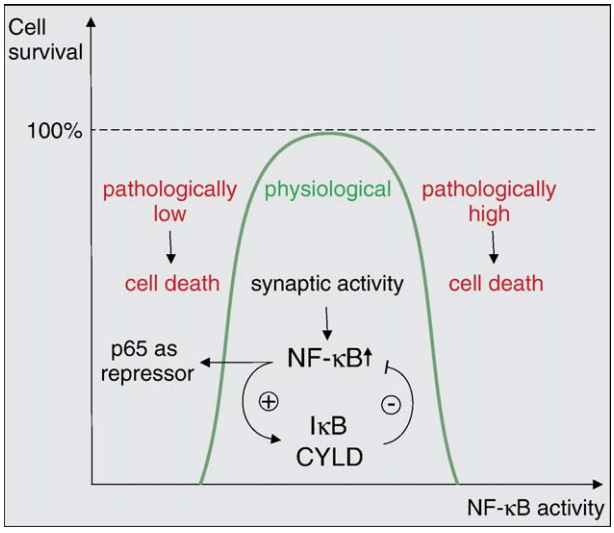

Fig. 3. Model for NF-κB homeostasis. Ongoing synaptic transmission might provide the permanent activation signal for constitutively active NF-κB in neurons. A physiological activation state could be maintained via an autoregulatory loop to the expression of NF-κB inhibiting proteins such as IκB family members or de-ubiquitinating enzymes, e.g., CYLD or A20. A perturbation of this physiological NF-κB activation might be pathological with the resulting cell death. The p65-mediated transcription of anti-apoptotic genes through the recruitment of co-activators (histone acetyltransferases) promotes survival under physiological conditions. Under pathophysiological conditions, p65 could be switched to a promoter selective dominant repressor of anti-apoptotic genes. This switch to a repressor might be mediated by the recruitment of co-repressors (histone deacetylases). This might be an additional mechanism for generating pathological low NF-κB level.

named amyloid precursor proteins (APP) [161]. Under normal conditions, the most abundant Aβ isoform is Aβ 1–40; however, much of the fibrillar Aβ is composed of the longer Aβ 1–42 isoform [162]. Initially Aβ 1–42 is deposited in the form of an immature diffuse plaque, with no or little neuritic distrophy [162]. In control subjects, NF-κB activation could be detected around all plaque types including diffuse and neuritic plaque stages (primitive, classical and compact) [51]. In Alzheimer patients, NF-κB activation around all analyzed plaque stages was reduced. Plaques were classified as diffuse and neuritic (primitive, classical and compact); see Kaltschmidt et al. [51].

In respect of this, it is noteworthy that the NF-κB signaling pathway is one of the major neuroprotective pathways identified to be protective against Alzheimer's disease (see [163] for a detailed discussion). A reduction of this protective NF-κB activation within Alzheimer patients' brains around late plaque stages might be one of the reasons for increased neurodegeneration [51].

A low dose of Aβ was able to activate NF-κB and to protect against a high cytotoxic dose of Aβ. This led to the discovery of an essential role for NF-κB in preconditioning [55,164,165]. Preconditioning describes an old observation worded by Paracelsus as "Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding' kein Gift ist" (all things are poisons, only the dose makes the poison). In this line, a toxin in a low dose could activate a cellular response program, which later on protects against a high dose of toxin. We think that the mechanisms might be similar to a process described by David Baltimore as intracellular immunization [166] against virus infection. The preconditioning effect of NF-κB could be completely abolished by the overexpression of transdominant IκB-α. On the other hand, there are toxic stimuli such as staurosporine where repression of NF-κB activation was protective [115]. This might be a general concept, which we first described in non-neuronal cells: The nature of the apoptotic stimulus dictates the pro- or anti-apoptotic action of NF-κB [167]. Genetic evidence suggests that constitutive NF-κB activity is essential for neuronal survival [152]. Similarly, pharmacological repression of the IKK complex ([168]; B. Kaltschmidt et al., unpublished) results in neuronal death. The transgenic overexpression of transdominant IκB-α sensitizes neurons against excitotoxic lesions [151]. NF-κB activation protects neurons against Aβ toxicity [51,54]. This might be a neuroprotective mechanism which is perturbated during Alzheimer disease [163]. On the other hand, several diseases where NF-κB hyperactivation is disease promoting are described. Examples include ischemia [82], Parkinson [169] and conditions were NF-κB-dependent p53 transcription mediates neuronal death [168]. The p53-mediated cell death seems to rely on a repression of NF-κB activity [170] in some paradigms.

To sort this dilemma out, an optimal activation hypothesis (Fig. 3) is proposed similar to the NMDA receptor activation [171]. Too low activation of NF-κB in neurons is disastrous, as is too high activation (hyperactivation). The optimal basal constitutive level in neurons is maintained by synaptic activity, which activates NF-κB and is repressed by one of its target genes IκB or CYLD in an auto-regulatory fashion (see Fig. 3). A potential protective role of NF-κB in neurons should be discriminated from a potential degenerative role in glia.

Acknowledgements

The work in our laboratory was supported, in part, by grants from the Deutsche Forschungsgemeinschaft (DFG), the Volkswagen-Stiftung and the Land NRW.

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